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RELATIVE EFFECTS OF X-RAYS AND NEUTRONS ON CHROMOSOMES IN DIFFERENT PARTS OF THE "RESTING STAGE"

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Introduction.—When rapidly growing plant or animal tissues are treated with x-rays or with neutrons, it has been observed that at three hours after treatment the per cent anaphase cells showing no chromosome abnormalities is a negative exponential function of the dose.[1] It was demonstrated that these cells were at the onset of prophase at the time of irradiation. The ratio of the slope of the curve obtained with neutrons to that obtained with x-rays was approximately six for all species studied.[2] The constancy of this ratio was taken as evidence of the similarity of the structural and physiological conditions in the chromosomes of the different species at this stage. The investigations reported here show that within a single species the value of the neutron x-ray ratio varies for chromosomes irradiated in different parts of the resting stage and consequently that the conditions with respect to radiation response vary during this morphologically homogeneous stage of the nuclear cycle.

Materials and Methods.—The conditions for germination and irradiation with x-rays were the same as described in previous experiments and the same lot of seed of *Vicia faba* was used. For neutron studies the seedlings were arranged on a holder so that the root tips were in a collimated beam of neutrons produced by bombarding a beryllium target with 16 million volt deuterons with the 60-inch cyclotron.[3] The dose was measured in arbitrary "n" units as previously described.[2] I am indebted to Dr. P. C. Aebersold for measuring the neutron doses and to Miss Addi van Nouhuys for assistance in preparing slides and making counts. Root tip smears were prepared at 8, 12, 18 and 24 hours after irradiation. Only cells in mid anaphase and late anaphase, where the ends of the disjoining chromosomes were well separated from each other, were counted. Such cells were classified into two categories. Those showing no chromosome abnormalities

were called normal. Those showing one or more chromosome attachments or fragments were listed as abnormal.

Results.—The data obtained are tabulated below. Seven doses were given in duplicate and one in triplicate. These all agreed within less than 5 per cent with one exception, where the difference was about 7 per cent.

TABLE 1

TIME IN HOURS	X-RAYS DOSE—r	NORMAL	ABNORMAL	% NORMAL	NEUTRONS DOSE—"n"	NORMAL	ABNORMAL	% NORMAL
8	0	606	7	99.0	0	398	7	98.2
	50	579	131	81.5	5	1015	471	68.5
	50	270	81	77.0	10	907	614	59.6
	50	697	200	77.8	10	253	231	52.4
	102	63	63	50.0	15	188	276	40.6
	100	405	340	54.4	20	218	440	33.2
	150	88	161	35.5	25	66	238	21.7
	200	45	143	23.9	30	57	246	18.8
	250	6	40	13.1	30	31	106	22.6
	400	2	26	7.1	40	7	62	10.2
12	0	402	5	99.0	0	112	3	97.4
	55	1432	300	82.7	5	866	289	75.0
	50	215	39	84.6	10	662	579	53.2
	100	681	217	76.0	20	197	396	33.3
	200	292	270	52.0	20	168	371	31.2
	300	88	142	36.6	23	245	529	31.8
					29	94	300	23.8
					32	104	406	20.4
					44	24	114	17.4
					60	1	17	5.5
18	0	429	5	99.0	0	374	10	97.5
	50	362	47	88.6	5	470	141	77.0
	100	400	181	68.9	20	332	247	57.4
	122	438	210	67.6	20	298	190	61.1
	200	143	131	52.2	30	269	377	41.6
	300	111	190	36.9	40	210	428	33.0
	300	164	318	34.1	40	259	618	29.6
	400	60	171	26.0	50	157	473	24.9
	500	35	146	19.3	70	123	647	16.0
24	0	655	5	99.3	0	1214	14	99.0
	50	394	30	93.2	10	128	51	71.5
	122	475	142	77.0	20	768	740	51.0
	130	757	304	71.3	30	94	227	29.2
	200	304	162	65.2	30	53	115	31.6
	300	209	217	49.0	45	55	233	19.1
	400	63	106	37.2	61	25	212	10.6
	500	117	203	36.6				

In figure 1 the logarithm of the per cent normal anaphases is plotted against dose in roentgens and in figure 2 against "n" units of neutron ion-

ization. It is clear that at each time interval for x-rays and for neutrons the points are best fitted by a straight line through the origin.

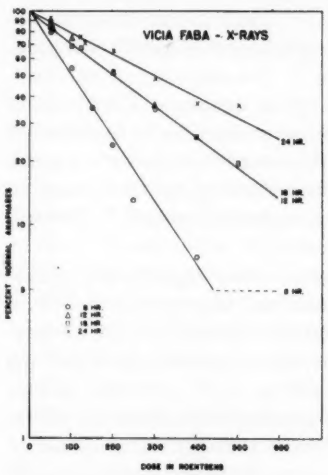

FIGURE 1

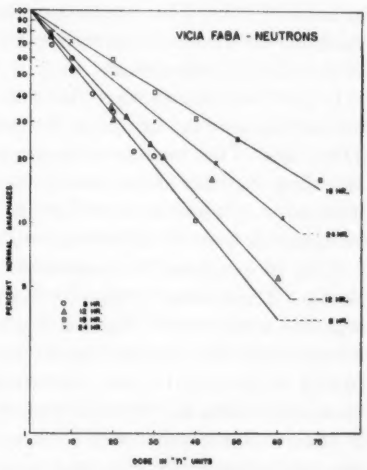

FIGURE 2

Fitting the lines graphically to the points, the slopes obtained are given in table 2. The values for three hours after irradiation are those which have previously been published.

TABLE 2

SLOPES OF SURVIVAL CURVES

HOURS AFTER IRRADIATION	NEUTRONS	X-RAYS	NEUTRONS/X-RAYS
3	7.0×10^{-2}	1.1×10^{-2}	6.4
8	5.6×10^{-2}	6.9×10^{-3}	8.1
12	5.0×10^{-2}	3.3×10^{-3}	15.1
18	2.8×10^{-2}	3.3×10^{-3}	8.5
24	3.7×10^{-2}	2.2×10^{-3}	16.8

The observed negative exponential between the logarithm of the per cent *normal* anaphases and the dose means that the number of chromosome *abnormalities* produced is proportional to the dose when allowance is made for multiple hits in chromosomes of the same cell. As previously pointed out, the exponential survival curves indicate that a single effective agent produced by the x-rays or neutrons is sufficient for producing a chromosome abnormality.[1, 2] These results do not agree with those obtained by Sax, who found that chromosome aberrations in Allium and Tradescantia

increased as the 1.5 power of the x-ray dose.[4, 5] They do agree with those of Giles[6] for neutron effects on chromosomes of Tradescantia observed 30 hours after treatment, and with those of Creighton[7] for Chorthippus chromosomes 3 hours after irradiation with x-rays. These investigators did not examine the chromosome response as a function of dose in different parts of the nuclear resting stage.

It has been shown that the cells observed in anaphase 3 hours after irradiation were at the end of the resting stage at the time of irradiation.[1] This phase of the nuclear cycle was called the onset of prophase. One can also show that the chromosome abnormalities observed between 3 and 13 hours after irradiation were all in the resting stage when treated. This will be apparent from the following considerations.

Cells in anaphase 24 hours after irradiation show degenerating micronuclei. These arise originally from chromosome fragments which form separate small nuclei, the size depending on the number and size of fragments included. During the resting stage, chromonematic structure can clearly be discerned in the micronuclei as well as in the principal nucleus. However, during the prophase they become pycnotic and eventually diffuse in their staining properties. They may persist through the anaphase or lose their chromaticity to such an extent as to be barely distinguishable from the cytoplasm. Such degenerating micronuclei are not seen in anaphase as late as 18 hours after irradiation. It follows, therefore, that these cells were in the resting stage at the time of irradiation and the 24-hour cells were in some stage of the preceding nuclear cycle. (Since micronuclei must be attributed to abnormalities previously formed, they were not included in counts of chromosome abnormalities.) Comparison of the slopes of the neutron and x-ray curves (n/x) for the interval 3–18 hours may then be used as an index of the relative sensitivity of the different portions of the resting stage to these agents. Such a comparison shows that the relative sensitivity to x-rays and neutrons varies by as much as a factor of two, and if the cells at 3 hours are included, by a factor of three.

One striking difference between the neutron and x-ray results is the steeper slope at 24 as compared with 18 hours in the case of neutrons but not with x-rays. Also at this time n/x is the highest observed (16.8). As explained above, the chromosomes in anaphase 24 hours after irradiation must have been in the preceding nuclear cycle when treated. The particular stage they were in is unknown, but since the time from the last resting stage corresponds to that for the interval from onset of prophase to anaphase, it may have been in the onset of prophase. The results therefore indicate that cells in which a chromosome abnormality has been produced by neutrons are much more likely to show another chromosome abnormality in the second succeeding anaphase than similar cells treated with x-rays. An adequate explanation for this observation may be found in a considera-

tion of the distribution of ionization of a proton track as compared with a beta-particle. If an abnormality is produced when the sensitive portion of a chromonema is transsected by a proton which produces one ion pair in the sensitive volume, we may expect more energy to be released in the immediate vicinity, unless the diameter of this volume were much smaller than the average spacing of ion pairs along the track. This has been shown not to be the case (i.e., the diameter of the sensitive volume is of the same order of magnitude as the spacing of ions in a proton track, 10^{-7} cm.). The distance between ion pairs along a beta-particle track is 10^{-5} cm. and an effect by the second ion pair, therefore, is much less probable. Thus a cell showing abnormalities at 3 hours after irradiation is more likely to show abnormalities in the succeeding anaphase (21 or more hours later) than a cell with the same number of abnormalities produced by x-rays. Nishina and Moriwaki[8] have found unusually high frequencies of multiple mutations and chromosome aberrations in a single chromosome following neutron treatment of Drosophila, which is in accordance with the hypothesis given above.

As mentioned previously, n/x for chromosomes 3 hours after irradiation is consistently 6 in tissues as different as tomato root tips and mouse tumors. However, with the same chromosomes in different parts of the resting stage, n/x varies by a factor of at least two. Conditions within the chromsome must, therefore, be changing. Thus, in the nuclei which take 12 hours to reach anaphase, the intrachromosomal structures which respond to x-ray or neutron ionization differ from those of nuclei which take 3 hours. Previous experiments have shown that the sensitivity of the 3-hour nuclei to x-rays may be markedly altered by pH, but not in the 5 to 36-hour nuclei, indicating a difference in the mechanism of response of the two types of nuclei. It was suggested that the greater sensitivity to x-rays and the response to pH of the 3-hour nuclei was due to the presence of closely approximated charged surfaces formed by the division of the chromonemata at this time.[9] Accepting this hypothesis, the difference in relative susceptibility of 8, 12 and 18-hour nuclei remains unexplained. If, in order to produce a chromosome abnormality by irradiation of chromosomes in the resting stage, it is necessary for the ionization or excitation to break several chemical bonds, the probability of multiple breakage will be greater with neutrons than with x-rays.

At least two different physiological states in the "resting" nucleus may now be identified. One, 18 hours prior to anaphase, shows a sharp maximum in the formation of half-chromatid fragments which was attributed to a critical stage in the synthesis of new chromonemata.[16] The other is the 12-hour peak in neutron sensitivity described above. The greater efficiency of neutrons in the 12-hour nuclei where the synthesis is more complete may then be due to the presence of fewer of the less stable bonds pres-

ent at 18 hours and at 8 hours where the chromonemata are preparing for the actual separation which is observed 5 hours later.

Timoféeff-Ressovsky and Zimmer[11] found that neutrons were less efficient than x-rays in producing recessive lethal mutations in Drosophila. Dempster[12] has found that although neutrons are less efficient in producing recessive lethal mutations they are more efficient in producing dominant lethals and translocations. If production of a visible mutation requires alteration of only a single bond while a dominant lethal (deficiency) requires alteration of several as in the case of the microscopically observed chromosome abnormalities, the genetic results and the cytological data can both be accounted for by the hypothesis just advanced.

A theory for the mechanism of chromosome response to ionizing radiation at the onset of the mitotic prophase and the pachytene stage of meiosis has been proposed[13] and supported by subsequent investigations.† Another theory postulating an initial chromosome breakage followed by fusion or "healing" of broken ends has been applied to chromosome response at all mitotic stages.[4, 5, 16] The variation in the ratio n/x with the stage of mitosis indicates that the simple breakage-healing hypothesis is inadequate. It fails to explain why chromosomes taking 3 hours to reach anaphase are more sensitive to x-rays or neutrons than the thinner, and therefore, presumably more delicate ones which take 8 or 18 hours. It also fails to explain why chromonemata which take 12 hours to reach anaphase and are, therefore, less developed and thinner than those which take 8 hours should show a greater relative response to neutrons. If differential healing is invoked, it is difficult to explain why chromosomes taking 3, 8 and 18 hours to reach anaphase show relatively greater amounts of healing following neutron treatment than chromosomes which take 12 hours.

Since n/x increases during the resting stage, it follows that independently of the units used to measure x-rays and neutrons, the latter are capable of producing more abnormalities in resting nuclei than x-rays. This result is of interest in x-ray and neutron therapy, for it suggests that neutrons may produce regression of tumors resistant to x-rays. The amount of damage to skin in comparison with a given amount of tumor regression may be different from that observed with x-rays. The value of the "erythema dose" in terms of tumor response, therefore, needs to be independently determined in neutron therapy. Likewise, the daily "safe dose" in terms of equivalent ionization may be considerably lower with neutrons than with x-rays.

Summary.—1. The logarithm of the per cent normal anaphase chromosomes is a negative exponential function of the dose of neutrons or x-rays in different parts of the nuclear cycle. Chromosome abnormalities are (i.e., if allowance is made for multiple hits) therefore directly proportional to the dose at all stages studied.

2. The ratio of neutron to x-ray efficiency (n/x) is constant for different species at the onset of prophase, but increases by a factor of at least 2 during the nuclear resting stage of a single species.

3. Increase in n/x during the resting stage indicates: (*a*) Conditions for chromosome response are not constant during resting stage. (*b*) The intrachromosomal structure responding to ionization may be different for the different parts of the nuclear cycle and resting stage. A theory invoking a single mechanism for the production of chromosome abnormalities is not adequate. (*c*) The relative effect of neutrons on chromosomes in the resting nucleus is greater than with x-rays. (*d*) Neutron therapy may produce regression in tumors which do not respond to x-rays. (*e*) The daily "safe dose" for exposure to neutrons may be considerably less than for x-rays.

4. The use of neutrons and x-rays as described furnishes a method for identifying the functional stages in the nucleus which cannot otherwise be identified.

5. The bearing of these results on theories concerning the mechanisms of the action of ionizing radiations is discussed.

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† See references 1, 2, 9, 10, 14 and 15 below.

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COMPARATIVE RATES OF DIVISION IN LARGE AND SMALL CELLS OF DEVELOPING FRUITS

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The relation of the size of a meristematic cell to its rate of division is an important problem in any analysis of growth and differentiation. A simple way to attack it is to determine the increase in number of cells in large-celled and in small-celled tissues of the same organ during a given period of growth. The early developmental stages of the cucurbit ovary provide good material for such a study. Its tissues are clearly delimited, and their volumes may thus be determined with some accuracy. Most of their constituent cells are relatively undifferentiated parenchyma. Cell volumes differ markedly in different tissues. By dividing tissue volume by cell volume, the approximate number of cells may be calculated for each tissue, and thus the comparative increase in cell number in large-celled and small-celled tissues, as growth proceeds, may be found.

In twelve inbred lines of cucurbits, belonging to four genera, tissue volumes and cell volumes were measured in ovaries with diameters of 2 mm. and in ovaries with diameters of 10 mm. In this stage of ovary development cell division is still going on throughout the organ. The tissues measured were the placental region, occupying the central portion of the ovary; the inner wall, extending from the placenta to the ring of main vascular bundles; the outer wall, extending from the bundle ring to the epidermis; and the epidermis itself, a single cell layer over the whole ovary. The ovary is essentially spherical and its structure was treated as a series of concentric spheres. Placental volume was calculated directly from placental diameter. Inner wall volume was found by subtracting this placental volume from the volume of a sphere of which the diameter was that of the bundle ring. The volume of the latter sphere subtracted from total ovary volume gave the volume of the outer wall. Average cell diameters (parenchymatous cells only) for these tissues had previously been reported in these same 12 lines.[1] Cell number has now been calculated for each tissue by dividing cell volume (cell diameter cubed) into tissue volume. In the epidermis, where cell division takes place only perpendicularly to the ovary surface, cell number was determined by dividing cell area (diameter squared) into area of ovary surface. These cell numbers are only approximations to the actual numbers but for purposes of comparison they are satisfactory and the consistent relationships which they show give confidence as to their essential accuracy.

There is a gradient of increasing cell volume from the outer tissues to

the inner ones. In the 2-mm. ovary the cells of the outer wall are about 2.2 as large as those of the epidermis, the cells of the inner wall 3.3 as large, and of the placenta 7.4 as large. In the 10-mm. ovary there has been a marked increase in cell volume except in the epidermis and the gradient is steeper, cells of the outer wall being about 5 times the volume of the epidermis, those of the inner wall 12 times, and those of the placental region over 40 times. These constant differences in cell volume between meristematic tissues show that the size to which a cell enlarges before it divides again is characteristic for a given tissue at a given stage of development. The problem is to determine whether this size is related to the rate of division.

In table 1 are given the average values, for the four tissues in the twelve lines, as to cell volume and number in the 2-mm. ovary, cell volume and number in the 10-mm. ovary, and ratio of increase in cell number (number at 10 mm. divided by number at 2 mm.). The latter value serves as a measure of comparative rate of cell multiplication in these tissues. The number of cell generations (and thus the number of divisions in each cell lineage) was found by determining the power of 2 which would give the observed ratio of increase.

TABLE 1

RELATION OF CELL SIZE TO INCREASE IN CELL NUMBER

	OVARY DIAMETER 2 MM.	OVARY DIAMETER 10 MM.	RATIO OF INCREASE IN CELL NUMBER	NUMBER OF CELL GENERATIONS
Epidermis				
Cell volume	1037 cu. μ	1498 cu. μ		
Cell number	139,346	3,115,670	22.90	4.52
Outer wall				
Cell volume	2362 cu. μ	7636 cu. μ		
Cell number	581,566	14,955,033	25.84	4.69
Inner wall				
Cell volume	3494 cu. μ	17,724 cu. μ		
Cell number	646,362	17,035,513	26.18	4.70
Placental region				
Cell volume	7713 cu. μ	65,148 cu. μ		
Cell number	133,670	3,324,341	25.00	4.64

It is evident that the ratio of increase in cell number, and thus presumably the rate of cell division, is essentially the same in all tissues and bears no relation to the initial size of the cells in the tissue or to the amount of increase in cell size as growth proceeds. That increase in cell number in the large-celled tissues is actually due to the division of these large cells rather than of small ones which might be scattered among them is indicated by the fact that the range in cell size in a tissue is not great, and that

mitotic figures and newly formed cell walls are frequent in these large cells. The author[2] has recently shown that relatively large, vacuolate cells like those here discussed commonly divide in meristematic regions.

For this material, at least, there is no relation between the volume of a cell and the rate at which it divides. In larger cells, the amount and rate of cell expansion, from the time when a new daughter cell is formed until this cell is ready to divide again, is evidently greater than in smaller cells. Whether this increase is in protoplasm or only in the size of the vacuole is not known.

Rate of cell division seems to be determined by some factor independent of cell size and operative throughout the entire organ.

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CHROMOSOME DEGENERATION IN RELATION TO GROWTH AND HYBRID VIGOR

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In the twenty-five years of genetic research, since hybrid vigor was put on a Mendelian basis,[9] additional evidence has accumulated from many sources that contributes toward a further solution of this problem. While much of this new information confirms the original hypothesis an important situation is brought to light which was not fully visualized in the early days of genetic investigation and shows where additional information is needed both for a more complete understanding of the principles involved and for the best application of hybrid vigor to practical breeding.

Both Shull and East showed clearly that the greatest vigor, generally, is exhibited when germinal heterogeneity is at the maximum. When this diversity is reduced by Mendelian recombination vigor is lost. The phrase "stimulus of heterozygosis" was contracted to the word "heterosis" by G. H. Shull[23] (1914) and was considered by Shull, East and other investigators at this time to be something additional to the normal expression of hereditary characters. They assumed that it could not be fixed and would therefore never be exhibited by organisms when in the homozygous condition. An interaction of diverse nuclear elements within an unfamiliar cytoplasm was postulated by A. F. Shull[22] (1912) as a possible contributing factor, based on evidence from rotifers. A revised form of the original hypothesis was put forth by East[6] (1936) which assumed an interaction between diver-

gent alleles. Evidence for this he found in segregating progenies of Nicotiana where few gene differences were involved. There was marked skewness in the frequency distributions of size characters but the extreme plus variants were impossible to fix whereas less difficulty was encountered in stabilizing minus variants. Allelic differences in the heterozygous condition in Nicotinana have shown a variation from each parental type that under cortain conditions might be advantageous[10] (Jones, 1921). Dunn[4] (1937) describes lethal alleles in mice that interact to give viable heterozygotes. In Godetia, Hiorth[8] (1940) has found that alleles have an additive effect as postulated by East. But the evidence, so far available, does not indicate that this type of interaction has an important part in the production of hybrid vigor.

All stimulation hypotheses, based on heterozygosis, ignore the fact that many plants that are almost completely self-fertilized in every generation are still the most efficient producers in the list of cultivated plants and many closely bred wild species of both plants and animals show no lack of ability to main themselves under natural conditions. Several cases are on record where recombination produces homozygous individuals that are equal or nearly equal to the hybrids from which they came as Malinowski[15] (1935) has shown in Phaseolus and Sveschnikova[25] (1940) in Vicia. Dodge[3] (1942) has obtained a recombination of growth-promoting genes in haploid Neurospora where heterozygosis is not involved. By back-crossing maize hybrids to one parent in successive generations and then crossing by the other, Richey and Sprague[19] (1931) have evidence for an increased or equal growth with reduced heterozygosity in the same gene complex. On the other hand Randolph[18] (1942) has found that tetraploid maize heterozygoes are relatively more vigorous than tetraploid homozygotes and this may be good evidence for an interaction between dissimilar genes. But it may also be simply an abnormal situation in which the weaker homozygotes are at a disadvantage while the much more vigorous heterozygotes are not.

From all the evidence at hand homozygous organisms are as well able to live as heterozygous forms and there is no necessity to assume any inherent physiological advantage in germinal association of dissimilar elements, in itself, for which the term, heterosis, was originally devised. The word continues to be used and has become practically synonymous with hybrid vigor. A third of a century of biological research has failed to bring forth any clear evidence in support of the stimulation theory. On the other hand, there is much new evidence to show that dominance and an accumulation of favorable heredity are the principal factors involved.

When naturally cross-fertilized organisms are inbred many defective and abnormal individuals are brought to light as is well known. Natural selection removes most of these and in any breeding program they are always selected away from unless valued for some particular purpose. Inbred

progenies after these defective and subnormal individuals are eliminated are still much reduced in size and in ability to grow and to reproduce. This is particularly true in maize, many other naturally cross-fertilized plants and nearly all domesticated animals. When unrelated inbred families are interbred there is an immediate rise in the growth level. The elimination or suppression of these visible abnormalities apparently has little to do with this phenomenon. This has led East[6] (1936) to say that "the elimination of deleterious recessives is of little importance in practical breeding and of no consequence whatever in the solution of the problem (of heterosis)."

This statement may be true for the defective genes that have a visible effect and can be eliminated but it is certainly not true for the non-visible defectives that are wide-spread in all cross-fertilized organisms and cannot be eliminated entirely by any method of selection now known. Heretofore their number and importance have not been appreciated. They can be detected only in favorable material when studied in such a way as to separate their action from that of all the remaining inherited complex, as recent investigations show clearly.

Many deficient loci in the corn chromosomes remain after long-continued inbreeding has eliminated the visible defectives. They exist in the homozygous condition but do not produce any distinct effect and are not as yet classified as Mendelian genes. They are similar in action to the visible defectives in that they reduce or slow physiological activity. In the long-continued self-fertilized lines of corn grown at the Connecticut Agricultural Experiment Station for more than 30 years, changes have taken place that delay flowering of certain progenies without otherwise altering their size. Other transmissible alterations reduce the size of the ear and height of the plant. None of these segregate clearly and the effects of any one are so small that they have been overlooked up to the present time.

Radiation experiments with many organisms show that chromosomes are frequently made deficient in the ability to transmit normal growth. Beadle and Tatum[1] (1941) irradiated the fungus, Neurospora, and found strains that lack the ability to produce certain growth-promoting substances. When chromosomes are broken and rearranged there is frequently a reduction of normal efficiency accompanying the break. While the evidence is far from complete it seems probable that many breaks, both natural and induced, reunite in the original arrangement but with various degrees of deficiency or derangement at the place of rupture. Whether the alteration precedes or follows the break is not important for the problem at hand. In Drosophila, collected from the wild, Dobzhansky and Queal[2] (1938) determined that about 39 per cent of the third chromosomes have loci that reduce viability below normal as compared with 2 per cent that raise it, and 3.5 per cent with visible external effects. Spencer[24] (1942) calculates that one detectable mutant is present in the heterozygous form

in about every four flies tested, varying somewhat in different species. This situation is probably the same, to a greater or less degree, in all naturally cross-fertilized organisms.

In naturally self-fertilized plants any hybrid vigor effect must be added to an already high level of productiveness. In plants like maize that are markedly reduced by inbreeding, the invigorating results of crossing are much more apparent. The extensive program of corn improvement by crossing inbred strains which has given such notable practical results in recent years has also brought forward evidence of much theoretical import. Well over 25,000 inbred strains of corn have been produced. Out of these, several hundred have been selected and are being used in the commercial production of hybrid corn in all parts of the country. The production of even the best of these inbreds does not exceed, and seldom approaches, 50 per cent of the yield of the original variety from which they were derived.[13] (Lindstrom, 1939). The few inbreds which are most widely used are not the most productive. In fact, some are so weak and unproductive that inbred seed cannot be produced regularly in those sections where their hybrids are most commonly grown. Many investigations have shown clearly that the ability to transmit yield is not closely correlated with characters visible in the inbreds.

Any two of these selected inbreds, if they are unrelated, can be crossed to give a marked increase in size of plant and yield of grain. Not all combinations have been tested but a sufficiently large sample has been tried to show that heterosis is practically universal among them. Some combinations are much better than others. In fact, the inbreds themselves are largely selected for their ability to give valuable hybrids. All of the hybrids are either within or close to the normal range of 80 to 120 per cent of the yield of the original varieties from which the inbreds were derived, well out of the 20 to 40 per cent range that the inbreds themselves are in. Any one of these—*A*, *B*, *C* and so on—can be crossed to give a vigorous hybrid. Since inbred *B* combines with inbred *C* to give as good a hybrid as *A* and *B* or *A* and *C* then *B* and *C* must differ from each other as much as *A* does from *B* or *C*. Similarly it is evident that *A* differs from *D*, *E* and so on down the list of hundreds of inbreds. No limit is in sight to the number of homozygous inbreds all of which differ from each other in whatever it is that makes up the major heterotic effect.

Not only do all combinations of two inbreds behave in this way but also all combinations of three and four or more. Just as in the single crosses, having two inbred parents, many double crosses, with four inbred parents, are better than others using the same inbreds but these differences are of an entirely different order of magnitude than the differences between inbreds and hybrids. In their range of variation in yield, inbreds and hybrids of the same maturity season seldom meet and even when they overlap the

individuals of each group clearly fall into two distinct frequency distributions[11] (Jones, 1922). The coefficients of variability for weight of grain per plant, which sums up the ability of the plant to grow and is a measure of reproductive ability, are seldom significantly more for double crosses than for single crosses. The importance of this fact has not been fully recognized.

In the combination of $A\ B \times C\ D$, bringing together four inbreds by successive crosses, every combination of chromosomes from none of A and all of B to all of A, and none of B unite in fertilization with ten chromosomes of C and D origin similarly assorted. Not only are the chromosomes shuffled as units but they are also taken apart and reassembled piece by piece down to the smallest amounts of each chromosome that can be separated by normal crossing over. In the 32,000,000 acres of double-crossed corn grown in the United States in 1941, a large sample of every possible combination of chromosome parts from the original inbreds has been taken. The astounding fact that practically every one of these plants, when given suitable conditions in which to grow, is normally vigorous and productive, proves beyond doubt that every seriously defective locus in any part of the chromosome complex is prevented from having an appreciable effect. This extraordinary situation points clearly to the fact that there are an enormous number of loci where loss or derangement may occur.

After inbreeding, the lethals and the most serious defectives are automatically eliminated. The resulting inbred strains, as far as they can survive, are reduced to the inbred level of vigor. Their position within the range of variation, possible at this level, depends upon the number and nature of their invisibly defective loci, to a large extent, irrespective of the potentially good heredity they may carry.

When unrelated inbreds are crossed practically all defective loci are covered by normal alleles. Complete or nearly complete dominance is shown. Visibly defective genes have been tested and shown to have little or no effect on yield in the heterozygous condition.[12,16] (Jones and Singleton 1935; Mangelsdorf, 1926). If differences between heterozygous and homozygous normals do exist they are small and of little consequence. With their defective loci covered the heterozygotes are lifted from the inbred to the crossbred level of vigor. As long as these defects are kept covered, crossbred individuals are restored to a condition that is comparable to that shown by naturally self-fertilized plants. In this condition their normal heredity has a chance to operate. On this plane of normal growth the inheritance determines height of plant, diameter of stalk, time of flowering and maturity, heat and cold tolerance, resistance to insects and diseases, and so forth. In other words, the plants respond to the interaction of all those qualitative and quantitative characters that are governed by the many complementary, duplicate, cumulative and inhibiting genes

that have been studied in many plants and animals. Some of these show dominance and some do not. Genes that reduce or inhibit large size and most rapid growth are known. All of these working together determine the position of the hybrid individual within the range of variation at the normal level.

Many genes promoting the most efficient growth and reproductive ability are at least partially dominant. Robbins[20,21] (1940, 1941) has compared plant hybrids with their parental types in tissue cultures. The offspring have the ability of both parents to produce and to use growth-promoting substances, some of which are lacking in one or the other parent. Many instances of this pooling of hereditary resources are well known.

The inheritance of many quantitative characters has necessitated the assumption of an absence of dominance. To many geneticists it has seemed unreasonable to use dominance to account for one phenomenon and to assume a failure of dominance in a different situation. But the facts are clear that many individuals occupy an intermediate position when compared with their parents in many measurable characters, particularly those that are little influenced by the environment. East[5] (1916) crossed Nicotiana species with flowers differing in length. The first generation was close to the arithmetical mean of the two parents in this linear character. Flower size is little affected by the size of the plants or the environmental conditions in which the plants grow. But in this same material, heterosis is clearly shown in height of plant and in the number of flowers and seeds.

MacArthur[14] (1941) found tomato hybrids to be almost exactly intermediate in fruit size when measured by the geometric mean. Here the character measured is three dimensional. Powers[17] (1941) also studied a wide species cross in tomatoes and found partial dominance of small fruit size when measured by the arithmetic mean, also dominance of smaller number of fruits per unit of vine. But many tomato crosses show a large increase in total amount of plant growth and in early maturity of fruit. Hayes and Jones[7] (1917) found that some varietal crosses of tomatoes gave an increased number and average weight of fruit as well as earlier maturity while other crosses did not.

Naturally self-pollinated plants show heterosis which is lost in later generations. But when hybrid corn is allowed to interpollinate, or is again inbred, not only is there a reduction in the number of normal, favorable growth genes but also there is the uncovering of the many defective loci always present in every part of the chromosome structure. The plants not only segregate within the normal complex but are rapidly reduced to the level of vigor in which the homozygous inbreds operate. Here normal heredity has a limited opportunity to find visible expression. This is proved by the fact that many of the most valuable inbred strains of corn are themselves weak and unproductive, as mentioned previously. Since

they combine well with nearly all other strains they undoubtedly have good heredity but this is prevented from expressing itself because something essential is missing. All other inbreds apparently have what these good combiners lack. The fact that any part of the chromosome structure of one inbred can substitute for the homologous part from almost any other inbred shows that the mechanism must be fundamentally alike within the species. Only comparatively minor derangements keep the chromosomes from functioning at full efficiency. This renders improbable the necessity of assuming extensive differences in germinal construction. Otherwise many combinations would fail to give normal growth.

For the practical breeder the maintenance of homozygous inbred lines is a matter of serious concern. The possibility of continued production of degenerative loci must be guarded against by progeny testing or valuable lines will be lost or reduced to such a low level of vigor that they can be used only with difficulty. For theoretical genetics it is worth while to note that there is the possibility of continued degeneration. This takes place in crossbred as well as in inbred families and has nothing to do with inbreeding but is more apparent after consanguineous mating and more quickly eliminated. The prevention of chromosome degeneration and the elimination of defective loci after they are formed, in organisms not exposed to rigorous natural selection, is one of the major biological problems of the future.

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TEMPERATURE AND "SEX-RATIO" IN DROSOPHILA PSEUDOÖBSCURA

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The "sex-ratio" condition was found originally in some natural populations of *Drosophila affinis*[1] and subsequently in *D. obscura*,[2] *D. pseudoöbscura*[3] and certain other species. The offspring of a "sex-ratio" male consists, regardless of the genetic constitution of his mates, of daughters and few or no sons.

"Sex-ratio" occurs, so far as we know, only in species with two-armed *X*-chromosomes, and it is always inherited as though it were due to a gene located in the right (longer) limb of this chromosome. Any "sex-ratio" *X*-chromosome in race A of D. *pseudoöbscura* carries, however, three inversions in its right limb.[4] The nature of the association between the "sex-ratio" and these inversions is unknown. Nevertheless, the proximate mechanism of its action is reasonably clear; namely, in most of the first spermatocytes of "sex-ratio" males the *X*-chromosome is clearly quadripartite instead of bipartite; this chromosome undergoes two equational divisions, and all the resulting spermatids carry an *X*-chromosome. The *Y*-chromosome in the spermatocytes is strongly pycnotic, its centromere is inactive during the divisions, and the chromosome is eventually excluded from the nucleus and lost in the cytoplasm.[3] There is, however, a certain amount of variability in the spermatogenesis of "sex-ratio" males. Some spermatozoa come to carry an *X* and a *Y*, others only a *Y*, and still others neither an *X* nor a *Y*. The two latter classes give rise to the few sons that occur in the progeny of "sex-ratio" fathers. The *XO* sons are, of course, sterile.

Now it is well known that the sex chromosomes of animals frequently differ from the autosomes in their behavior at meiosis in the *XY* sex. They differ in two respects. The first of these is in the nucleic acid charge, which is frequently excessive in prophase and metaphase, as well as in the resting stage. The second is in the timing of the division cycle of the gene string and of the centromere; in the Heteroptera, for example, both of these seem to be advanced to give a coördinated suppression of pairing and crossing over and a division one mitosis ahead of the autosomes.[5] In Drosophila the excess charge is slight and the difference chiefly expresses itself in the mode of pairing and crossing over.[6]

The association of an increase in nucleic acid charge and hastening of division cycles we now know to be expected on more general grounds.[7] It

is to be inferred equally in "sex-ratio" *Drosophila*. *X* is supercharged enough to cause super-division. *Y* is presumably so much supercharged that its super-division cannot be seen. It is immobilized. The excessive nucleic acid charge goes, as it so often does, with a persistence of the nucleolus to metaphase.[8] This behavior, however, is slightly variable and might therefore provide a first means of testing the mode of action of a nucleic acid charge by experiment in the following way. In various plants

TABLE 1

NUMBER OF OFFSPRING AND PER CENT MALES IN "SEX-RATIO" CULTURES AT DIFFERENT TEMPERATURES

t°	SERIES	NUMBER OF CULTURES	INDIVIDUALS COUNTED	PER CENT MALES
25°	I	5	485	4.80
	II	5	663	6.03
	III	7	665	7.22
	IV	8	1263	6.02
	V	6	403	5.71
	VI	5	736	6.79
Total		36	4188	6.18
22°	I	7	2516	2.07
	II	8	2924	2.74
	III	14	3648	3.56
	IV	9	2309	2.99
	V	4	1066	3.75
	VI	12	3135	6.09
Total		54	15,598	3.74
16.5°	I	7	2102	0.67
	II	5	1994	1.05
	III	10	3969	1.18
	IV	7	2030	1.08
	V	8	2557	0.74
	VI	9	3010	2.19
Total		46	15,662	1.22

and animals which can be grown satisfactorily over a temperature range of 0°C.–25°C., it has been possible to show that the lower extreme of temperature reduces the nucleic acid charge at metaphase of mitosis and meiosis.[9,10] Such a range of temperature is too much to ask of the fly. But with the range that is possible, it would appear worth while to look for a change in "sex-ratio" behavior.

For the purposes of the experiment, a "sex-ratio" strain originally derived from the population of Andreas Canyon, Mount San Jacinto, Cali-

fornia, was used. This strain was perpetuated with the aid of the sex-linked recessives yellow, singed, vermillion, compressed and short (*y sn v co sh*) which served as markers. "Sex-ratio" is almost completely linked to *co*. Females of the constitution "sex-ratio"/*y sn v co sh* are normal wild type in appearance and breeding habit; they are crossed to *y sn v co sh* males in each generation.

A group of about six "sex-ratio"/*y, sn v co sh* females and an equal number of *y sn v co sh* males were transferred daily to fresh culture bottles. The bottles with the eggs deposited in them were divided into three groups. One group developed in an incubator at 25.0 ± 0.1° C. The second group was left in a room in which the temperature fluctuated irregularly from about 20° to 24°C., the average being close to 22°C. The third group developed in a cold room with an average temperature of 16.5° and four to five hourly fluctuations from 15° to 17°C. The wild type males hatching in these cultures must carry "sex-ratio." Five to six such males of each group were outcrossed to an equal number of females from a wild strain originating at Keen Camp, San Jacinto, California, which had developed in the cold room. The parents were transferred to fresh culture bottles daily or at two-day intervals. Oviposition took place at the same temperature at which the males had developed, but later all the cultures were kept together at room temperature. Complete counts of the offspring were made. We are indebted to Mr. B. Spassky for assistance in making these counts. A summary of the data is presented in table 1.

It is evident that "sex-ratio" is most extreme at the lowest temperature tried, 16.5°C., at which only 1.22 ± 0.09 per cent of the progeny are males. At room temperature the proportion of males rises to 3.74 ± 0.16, and at 25° to 6.18 ± 0.37 per cent. The differences are undoubtedly significant. Although all the experimental cultures contained flies of similar pedigree, we have recorded separately the series of cultures coming from the same group of parents. As shown in table 1, six such series have been raised at each of the three temperatures, the number of cultures per series ranging from 4 to 14. A study of variance discloses a significant non-homogeneity of the results in the different series, especially those kept at room temperature. Since, as stated above, the "room temperature" varied rather widely and irregularly, the observed non-homogeneity presumably indicates a great sensitivity of "sex-ratio" to temperature changes.

Thus the lower temperature seems to increase the frequency of *X*-sperm produced by "sex-ratio" males from 94 to 99 per cent. How this result comes about is another matter. The difference is too slight to make a cytological discrimination feasible. It may be assumed that any effect on the *Y* is irrelevant, and that it is only the regularity in double division of the *X* that is changed as temperature changes. Since this was the basis of our expectation it is to differences in the nucleic acid charge that we

must look for the effective agent in this change. In this respect the effect of temperature is the opposite to that found in Trillium and Triton. That in itself is not surprising, for in them the metaphase charge is concerned while in Drosophila it is the resting stage reproduction. And between resting stage and metaphase there is a reversal of charge in Trillium and Triton. Thus the two parts of the relationship: temperature—nucleic acid charge—division cycle, are seen pieced together, although how they are pieced together we do not yet know.

Summary.—The "sex-ratio" gene or complex in the X-chromosome of many Drosophila species causes the X-chromosome to divide twice at meiosis in the males while the Y is thrown out. This abnormality seems to depend on an excessive nucleic acid charge and should therefore (on other evidence) be affected by temperature. This expectation was confirmed. The proportion of X-sperm was reduced from 99 to 94 per cent by raising the temperature from 16° to 25°C.

* Experimental data by Th. Dobzhansky, the general interpretation by C. D. Darlington.

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*A GENERAL THEOREM ON THE INITIAL CURVATURE OF DYNAMICAL TRAJECTORIES**

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The theorem we intend to establish is an extension to acceleration fields of higher order of Kasner's dynamical theorem[1] which states that: *If a particle starts from rest in any positional field of force, the initial curvature of the trajectory is one-third of the curvature of the line of force through the initial position.*

We formulate this result analytically. If $\phi(x, y)$ and $\Psi(x, y)$ represent the rectangular components of a planar field of force acting at any point

(x, y) and t is the time, then the newtonian equations of motion for a particle of unit mass are

$$\frac{d^2x}{dt^2} = \phi(x, y), \quad \frac{d^2y}{dt^2} = \Psi(x, y).$$

If the curvature of the lines of force is everywhere zero, then the lines of force are straight lines, and a particle starting from rest at any point must necessarily move along the line of force. Thus, the trajectory and the line of force coincide and the theorem is trivially true. Excluding this degenerate possibility, we choose a point (x_0, y_0) at which the curvature of the line of force, which will be represented by Ω, is not zero. By direct calculation, we find that the curvature of the line of force, which line of force satisfies the differential equation $\frac{dy}{dx} = \frac{\Psi(x, y)}{\varphi(x, y)}$, is

$$\Omega = \frac{\varphi(\Psi_x\varphi + \Psi_y\Psi) - \Psi(\varphi_x\varphi + \varphi_y\Psi)}{(\varphi^2 + \Psi^2)^{3/2}}, \tag{1}$$

where the subscripts x and y denote partial differentiation and the functions φ, Ψ and their partial derivatives are evaluated at (x_0, y_0). If $\gamma_2(x_0, y_0)$ is the curvature of the trajectory of the particle which starts from rest at (x_0, y_0), then Kasner's theorem states

$$\gamma_2(x_0, y_0) = {}^1/_3\Omega.$$

The result we wish to prove is the following generalization.

THEOREM: *If a particle starts from "maximum rest" in an acceleration field of order n, the initial curvature of the trajectory is* $\frac{n!(n-1)!}{(2n-1)!}$ *times the curvature of the line of force through the initial position.*

Again, if $\phi(x, y)$ and $\Psi(x, y)$ are the rectangular components of a planar acceleration field of order n acting at any point (x, y) and t is the time, then the equations of motion for a particle of unit mass are

$$\frac{d^nx}{dt^n} = \varphi(x, y), \quad \frac{d^ny}{dt^n} = \Psi(x, y). \tag{2}$$

By the phrase "maximum rest," we mean that for $t = 0$, the initial conditions are

$$\frac{d^jx}{dt^j} = \frac{d^jy}{dt^j} = 0, \quad 0 < j < n;$$

that is, not merely is the initial velocity zero, but also all the initial accelerations of order up to and including $n - 2$ are zero.

As before, if the curvature of the lines of force is everywhere zero, then the lines of force are straight lines, and a particle starting from maximum rest at any point must move along the line of force through that point. Thus the trajectory and the line of force coincide and the theorem will be trivially true. Excluding this possibility, we choose a point (x_0, y_0) at which the curvature of the line of force is not zero. The curvature of the trajectory at (x_0, y_0) may be calculated from the formula

$$\gamma_n = \frac{\frac{dx}{dt}\frac{d^2y}{dt^2} - \frac{dy}{dt}\frac{d^2x}{dt^2}}{\left[\left(\frac{dx}{dt}\right)^2 + \left(\frac{dy}{dt}\right)^2\right]^{3/2}}. \tag{3}$$

However, as $\frac{dx}{dt} = \frac{dy}{dt} = 0$ for $t = 0$, γ_n assumes an indeterminate form and we must have recourse to the theory of limits in order to obtain the desired value. To achieve this, we expand the solution of (2) as power series in the time.

Let the parametric equations of the trajectory be

$$x = a_0 + a_1 t + \ldots + \frac{a_r}{r!} t^r + \ldots$$

$$y = b_0 + b_1 t + \ldots + \frac{b_r}{r!} t^r + \ldots$$

where the coefficients a_r, b_r are to be evaluated. From the initial conditions it follows immediately that

$$a_0 = x_0 \quad a_1 = a_2 = \ldots = a_{n-1} = 0, \quad a_n = \varphi(x_0, y_0)$$

$$b_0 = y_0 \quad b_1 = b_2 = \ldots = b_{n-1} = 0, \quad b_n = \Psi(x_0, y_0).$$

Differentiate equations (2) with respect to the time. This yields

$$\frac{d^{n+1}x}{dt^{n+1}} = \varphi_x \frac{dx}{dt} + \varphi_y \frac{dy}{dt}, \quad \frac{d^{n+1}y}{dt^{n+1}} = \Psi_x \frac{dx}{dt} + \Psi_y \frac{dy}{dt}.$$

Therefore, for $t = 0$,

$$\frac{d^{n+1}x}{dt^{n+1}} = 0, \quad \frac{d^{n+1}y}{dt^{n+1}} = 0$$

since $\frac{dx}{dt} = 0$ and $\frac{dy}{dt} = 0$. By repeated differentiations we find as initial values for the higher derivatives

$$\frac{d^{n+j}x}{dt^{n+j}} = 0, \quad \frac{d^{n+j}y}{dt^{n+j}} = 0$$

for all values of j less than n. However, for $j = n$, the appropriate initial values are

$$\frac{d^{2n}x}{dt^{2n}} = \varphi_x\varphi + \varphi_y\Psi, \quad \frac{d^{2n}y}{dt^{2n}} = \Psi_x\varphi + \Psi_y\Psi$$

with φ, Ψ and their partial derivatives evaluated at (x_0, y_0). Therefore,

$$a_{n+1} = \ldots = a_{2n-1} = 0, \quad a_{2n} = \varphi_x\varphi + \varphi_y\Psi$$
$$b_{n+1} = \ldots = b_{2n-1} = 0, \quad b_{2n} = \Psi_x\varphi + \Psi_y\Psi.$$

and the expansions for the equations of the trajectory are

$$x = x_0 + \frac{\varphi}{n!}t^n + \frac{\varphi_x\varphi + \varphi_y\Psi}{(2n)!}t^{2n} + \text{higher powers}$$

$$y = y_0 + \frac{\Psi}{n!}t^n + \frac{\Psi_x\varphi + \Psi_y\Psi}{(2n)!}t^{2n} + \text{higher powers.}$$

Substituting in formula (3) for the curvature, we obtain

$$\gamma_n = \frac{[\varphi(\Psi_x\varphi + \Psi_y\Psi) - \Psi(\varphi_x\varphi + \varphi_y\Psi)]\left[\frac{1}{(n-1)!(2n-2)!} - \frac{1}{(n-2)!(2n-1)!}\right]t^{3n-3} + \text{higher powers}}{[\varphi^2 + \Psi^2]^{3/2}\left[\frac{1}{(n-1)!}\right]^3 t^{3n-3} + \text{higher powers}}.$$

Taking the limit as $t \to 0$, and comparing with formula (1), we have the desired conclusion, namely

$$\gamma_n(x_0, y_0) = \frac{n!(n-1)!}{(2n-1)!}\Omega.$$

This completes the proof.

For the value $n = 2$, we obtain as a corollary Kasner's theorem,

$$\gamma_2(x_0, y_0) = 1/3\,\Omega.$$

For $n = 3$, we find $\gamma_3 = 1/10\,\Omega$; for $n = 4$, $\gamma_4 = 1/35\,\Omega$.

We notice that the ratio of any two successive values of the initial curvature takes the simple form

$$\frac{\gamma_{n+1}}{\gamma_n} = \frac{n+1}{2(2n+1)}.$$

Our general theorem (as in the special[1] case $n = 2$) is found to be valid in ordinary space of any number of dimensions and also in riemannian geometry.

* Presented to the American Mathematical Society, February, 1942.

[1] See Kasner, E., *Princeton Colloquium Lectures*, 1912, p. 9. Also: *Trans. Am. Math. Soc.*, 1906–1909; *Science*, **75**, 671 (1932); Zurich International Congress of Mathematics, **2**, 180 (1932); *Proc. Nat. Acad. Sci.*, **20**, 130 (1934); Fialkow, A., *Trans. Am. Math. Soc.*, **38**, 89 (1935).

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*GENERALIZED TRANSFORMATION THEORY OF ISOTHERMAL AND DUAL FAMILIES**

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The Isothermal Character Theorem.—A noteworthy theorem in the theory of functions of a complex variable is that the conformal transformations are the only *point* correspondences which carry every isothermal family of curves into an isothermal family. Kasner's generalization[1] of this result to the lineal-element transformations of the plane is

THEOREM 1. *The group of lineal-element transformations of the real plane which convert every isothermal family into an isothermal family is in cartesian coordinates* (x, y, θ)

$$X = \phi(x, y),\ Y = \psi(x, y),\ \Theta = a\theta + h(x, y), \tag{1}$$

where ϕ *and* ψ *satisfy the Cauchy-Riemann equations* (*direct or reverse*)

$$\phi_x = \pm\psi_y,\ \phi_y = \mp\psi_x, \tag{2}$$

and h *is any harmonic function of* (x, y), *and* a *is a non-zero constant.*

A corollary of this is that the only *contact* lineal-element transformations preserving the isothermal character are the conformal.

This theorem contains most well-known devices for obtaining isothermal families from a given isothermal family. In particular, there appear as special cases the facts that the isogonals and the multiplicatives of an isothermal family each form an isothermal family. However Theorem 1 does not contain the less familiar result that the isoclines of an isothermal family are an isothermal family. Our new generalization to field-element transformations will contain this fact as a special case.

We define a *field-element* of the plane by the number quintuplet (x, y, θ, r, s) where (x, y) are the cartesian coordinates of the point, θ is the inclination of the direction, $r = \theta_x$ and $s = \theta_y$. This may be represented geometrically as a lineal-element E of a field F together with the tangent flat field of F at E.[2]

Any field-element to lineal-element transformation T may be given by

$$X = \phi(x, y, \theta, r, s), \quad Y = \psi(x, y, \theta, r, s), \qquad \Theta = \chi(x, y, \theta, r, s). \quad (3)$$

We shall restrict ourselves to *admissible* transformations T. Any such transformation T carries any field with integral curves not all point-unions (stars) into any other such field. For any admissible transformation T, the functions ϕ and ψ are *not* functionally dependent. We also exclude the unimportant case where all fields, isothermal or not, are carried into a single isothermal field.

THEOREM 2. *The complete set of admissible field-element to lineal-element transformations which carry any isothermal field into an isothermal field is*

$$X = \phi(x, y, r, s), \quad Y = \psi(x, y, r, s), \qquad \Theta = a\theta + h(x, y, r, s), \quad (4)$$

where ϕ and ψ satisfy the Cauchy-Riemann equations (direct or reverse) (for each of the two complex variables $x + iy$ and $r - is$)

$$\phi_x = \pm\psi_y, \ \phi_y = \mp\psi_x, \ \phi_r = \mp\psi_s, \ \phi_s = \pm\psi_r, \quad (5)$$

and h is any biharmonic function, that is, h satisfies the four Poincaré partial differential equations of second order

$$h_{xx} + h_{yy} = 0, \ h_{xr} - h_{ys} = 0, \ h_{xs} + h_{yr} = 0, \ h_{rr} + h_{ss} = 0, \quad (6)$$

and a is a constant.

Next we study the *contact* field-element transformations of the plane. This is the complete set of field-element transformations which carry every field into a field.

THEOREM 3. *The entire group of contact field-element transformations which send every isothermal field into an isothermal field consists of the extension of the Kasner group (1), and the set of transformations*

$$r = \phi(X, Y, x, y), \ s = \psi(X, Y, x, y),$$
$$\Theta = a[\theta - \int \{r\,dx + s\,dy\}] + h(X, Y),$$
$$R = -a\int \{r_X dx + s_X dy\} + h_X, \ S = -a\int \{r_Y dx + s_Y dy\} + h_Y \quad (7)$$

where ϕ and ψ satisfy the Cauchy-Riemann equations

$$\phi_x = \psi_y, \ \phi_y = -\psi_x, \ \phi_X = \mp\psi_Y, \ \phi_Y = \pm\psi_X, \quad (8)$$

and h is a harmonic function of (X, Y), and a is a non-zero constant.

The field-element to lineal-element transformation by which every field is carried into its isocline field is

$$X = x,\ Y = y,\ \Theta = -\arctan r/s. \tag{9}$$

This transformation obviously comes under Theorem 2 but *not* under Theorem 3 since it is not a contact transformation.

The Dual-Isothermal Character Theorem.—Any system of ∞^1 curves which under the group of equilong transformations of the plane can be carried into the ∞^1 point-unions (stars) of a straight line has been called *dual-isothermal* by Kasner. A field, given in hessian coordinates (u, v, w) by $w = w(u, v)$, is dual-isothermal if and only if w satisfies the dual-Laplace equation $w_{vv} = 0$, that is, if $w = v\alpha(u) + \beta(u)$.

By the definition, any equilong transformation carries every dual-isothermal family into a dual-isothermal family. The generalization[3] of this result to lineal-element transformations of the plane is

THEOREM 4. *The group of lineal-element transformations which carry every dual-isothermal family into a dual-isothermal family is*

$$U = \phi,\ V = \frac{a_2v + b_2w + c_2}{a_1v + b_1w + c_1},\ W = \frac{a_3v + b_3w + c_3}{a_1v + b_1w + c_1}, \tag{10}$$

where ϕ, a_1, b_1, c_1, a_2, b_2, c_2, a_3, b_3, c_3 are functions of u only.

A corollary of this is that the *contact* lineal-element transformations preserving the isothermal character are

$$U = \phi(u),\ V = v\psi(u) + \chi(u),\ W = \frac{w\psi + v\psi_u + \chi_u}{\phi_u}. \tag{11}$$

This is a group of line transformations larger than the equilong group. We obtain the equilong group by imposing the condition $\psi = \pm\phi_u$.

A field-element of the plane may be defined by the number quintuplet (u, v, w, p, q), where (u, v, w) are the hessian coordinates of the lineal element E and $p = w_u$ and $q = w_v$.

Any field-element to lineal-element transformation T may be given by

$$U = \phi(u, v, w, p, q),\ V = \psi(u, v, w, p, q),\ W = \chi(u, v, w, p, q). \tag{12}$$

We restrict ourselves to admissible transformations T. Any such transformation T carries any field with integral curves not all straight lines into any other such field. For any admissible transformation T, the functions ϕ and χ are *not* functionally dependent. The unimportant case where all fields, dual-isothermal or not, are carried into a single dual-isothermal field is also excluded.

THEOREM 5. *The complete set of admissible field-element to lineal-element transformations which send any dual-isothermal field into a dual-isothermal field is*

$$U = \phi,\ V = \frac{a_2v + b_2p + c_2}{a_1v + b_1p + c_1},\ W = \frac{a_3v + b_3p + c_3}{a_1v + v_1p + c_1}, \qquad (13)$$

where ϕ, a_1, b_1, c_1, a_2, b_2, c_2, a_3, b_3, c_3 *are functions of* u, q, *and* $(w - qv)$ *only.*

Next we study the contact field-element transformations of the plane.

THEOREM 6. *The entire group of contact field-element transformations which convert every dual-isothermal field into a dual-isothermal field is*

$$U = U(u, q, \omega),\ Q = Q(u, q, \omega),\ W = QV + \Omega(u, q, \omega),$$
$$V = \frac{v(U_u\Omega_\omega - U_\omega\Omega_u) + p(U_\omega\Omega_q - U_q\Omega_\omega) + (U_q\Omega_u - U_u\Omega_q)}{v(U_\omega Q_u - U_u Q_\omega) + p(U_q Q_\omega - U_\omega Q_q) + (U_u Q_q - U_q Q_u)}, \qquad (14)$$
$$P = \frac{v(\Omega_\omega Q_u - \Omega_u Q_\omega) + p(\Omega_q Q_\omega - \Omega_\omega Q_q) + (\Omega_u Q_q - \Omega_q Q_a),}{v(U_\omega Q_u - U_u Q_\omega) + p(U_q Q_\omega - U_\omega Q_q) + (U_u Q_q - U_q Q_u)}$$

where $\omega = w - qv$.

The field-element transformation whereby every field is carried into its dual-isocline field is

$$U = u,\ V = v,\ W = -p/q. \qquad (15)$$

This comes under Theorem 5 but not under Theorem 6 since it is not a contract transformation.[4]

[*] Presented to the American Mathematical Society, February, 1942.

[1] Kasner, "Lineal Element Transformations Which Preserve the Isothermal Character," *Proc. Nat. Acad. Sci.*, **27**, 406–409 (1941). Conformal mapping obviously converts isothermal families into isothermals. But the converse, that no other point transformations can be successful, does not seem to appear in the standard literature; and was first obtained as a corollary of the search for element transformations in that paper.

[2] Kasner and De Cicco, "The Geometry of Turbines, Flat Fields, and Differential Equations," *Am. Jour. Math.*, **59**, 545–563 (1937).

[3] De Cicco, "Lineal Element Transformations Which Preserve the Dual-Isothermal Character," *Proc. Nat. Acad. Sci.*, **27**, 409–412 (1941).

[4] Whereas the isocline field of any field F is determined by the point-unions on the ∞^1 equiparallel series of F, the dual-isocline field of any field F is defined with respect to a given linear turbine T as follows: Let S_G be the series of intersection of F and any nonlinear flat field whose central element G is on T. The line-unions of these ∞^1 coflat series S_G form the dual-isocline field of F. Thus if (u, v, w) represent the *equilong* coordinates of a lineal-element, then the correspondence (14) represents the dual-isocline field of any field with respect to the linear turbine T whose elements all lie on the negative y-axis.

CONCERNING SEPARABILITY

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Axiom 1 of the author's Foundations of Point Set Theory[1] is as follows.

AXIOM 1. *There exists a sequence $G_1, G_2, G_3, \ldots$ such that (1) for each n, G_n is a collection of regions covering S, (2) for each n, G_{n+1} is a subcollection of G_n (3) if R is any region whatsoever, X is a point of R and Y is a point of R either identical with X or not, then there exists a natural number m such that if g is any region belonging to the collection G_m and containing X then $\bar{g}$ is a subset of $(R - Y) + X$, (4) if $M_1, M_2, M_3, \ldots$ is a sequence of closed point sets such that, for each n, M_n contains M_{n+1} and, for each n, there exists a region g_n of the collection G_n such that M_n is a subset of g_n then there is at least one point common to all the point sets of the sequence $M_1, M_2, M_3, \ldots$.*

Axiom 0 states that every region is a point set.

In this paper the following theorem will be established.

THEOREM 1. *If Axioms 0 and 1 hold true and there do not exist uncountably many mutually exclusive domains then space is separable.*

Proof. There exists a well-ordered sequence α whose terms are the regions of G_1. There exists a well-ordered subsequence α_1 of α such that (1) the first term of α_1 is the first term of α, (2) if β is a well-ordered subsequence of α_1 distinct from α_1 and such that every term of α_1 which precedes a term of β belongs to β then (a) there exists a region R belonging to α and intersecting no region of β and (b) the first such region R in α is the first term of α_1 following all the terms of β. Let H_1 denote the collection of all regions of the sequence α_1. The regions of H_1 are mutually exclusive and every point either belongs to H_1^* or is a limit point of it.[2] Similarly there exists a collection H_2 of mutually exclusive regions such that (1) H_2 is a subcollection of G_2, (2) if x is a region of H_2, $\bar{x}$ is a subset of some region of H_1, (3) if x is a region of H_1 every point of x belongs to, or is a limit point of, the sum of all the regions of H_2 which are subsets of x. This process may be continued. Thus there exists a sequence $H_1, H_2, H_3, \ldots$ such that, for each n, (1) H_n is a subcollection of G_n, (2) if x is a region of H_{n+1}, $\bar{x}$ is a subset of some region of H_n, (3) the regions of H_n are mutually exclusive, (4) if x is a region of H_n every region that intersects x intersects the sum of all the regions of H_{n+1} which are subsets of x.

Let H denote the set of all regions h such that, for some n, h belongs to H_n. Since, for each n, the regions of H_n are mutually exclusive, the collection H is countable. Suppose R is a region. There exists a region R_1 such that $\bar{R}_1$ is a subset of R. The region R_1 intersects some region x_1 of H_1. It also intersects some region x_2 of H_2 which is a subset of x_1. This process may be continued. Thus there exists a sequence of regions $x_1, x_2, x_3, \ldots$ such

that, for each n, x_n belongs to H_n, intersects R_1 and contains $\bar{x}_{n+1}$. But, for each n, x_n belongs to G_n. Hence the regions of this sequence have a point O in common. Suppose O does not belong to $\bar{R}_1$. There exists a number n such that if g is any region of G_n containing O then $\bar{g}$ is a subset of the domain $S - \bar{R}_1$, contrary to the fact that x_n contains O, belongs to G_n and intersects $\bar{R}_1$. Hence O belongs to $\bar{R}_1$ and therefore to R. It follows that, for some n, x_n is a subset of R. Thus every region contains some region of H. Since H is countable it follows that space is separable.

*Let Q denote the axiom obtained from Axiom 1 by replacing stipulation (4) concerning $G_1, G_2, G_3, \ldots$ in the statement of that Axiom by the stipulation that if x and y are regions such that $\bar{x}$ is a subset of y and $g_1, g_2, g_3, \ldots$ is a sequence of regions such that, for each n, g_n contains $\bar{g}_{n+1}$, belongs to G_n and intersects x then, for some n, g_n is a subset of y. By an easily made modification of the above proof, it may be shown that Theorem 1 remains true if, in the statement of its hypothesis, "1" is replaced by "Q."

Clearly Axiom Q holds true in every metric space. But, in the presence of Axiom O, it is weaker than Axiom 1. It has been shown, by John H. Roberts,[3] that Axiom 1 holds true for no metric spaces which are not complete. But there exist both separable and non-separable spaces which satisfy Axioms 0, 1, 2, 3, 4, 5_1, 5_2 and 6 and which are not metric. Consider the following examples.

Example 1. In a three-dimensional Euclidean space E, let β denote a definite straight line and let O denote a definite point lying on it. Let G denote the set of all point sets ("half-planes") g such that, for some plane M containing β, g is the sum of β and a component of $M - \beta$. There is a one to one correspondence between the points of β and the half-planes of the set G. For each point P of β let $T(P)$ denote the half-plane of G with which it is paired in this correspondence. For each point P of β let W_P denote the set of all straight line rays which start from P and lie, except for P, wholly in $T(O) - \beta$. If P is a point of β and a is a ray of $W(P)$, let $Z(a)$ denote the image of a under a rotation around β that throws the plane $T(O)$ into the plane $T(P)$. If P is a point of β, a and b are rays of W_P and ϵ is a positive number, let $R_{Pab\epsilon}$ denote a set such that x is an element of it only if either (1) x is the open curve $y + Z(y)$ for some ray y of the set W_P such that $y - P$ is separated from $\beta - P$ by $a + b$ in the half-plane $T(O)$ or (2) x is a point which is at a distance less than ϵ from P and which is separated from $\beta - P$ by $a + b$ in $T(O)$ or from $\beta - P$ by $Z(a) + Z(b)$ in $T(P)$.

Let Σ denote a space such that (1) X is a point of Σ if and only if either X is a point of $E - \beta$ or, for some point P of β, X is the open curve $a + Z(a)$ for some ray a of W_P, (2) R is a region of Σ if and only if either, in some half-plane of the set G, R is the interior of some circle containing no point of β or R is $R_{Pab\epsilon}$ for some P, a, b and ϵ. This space satisfies all of the above mentioned axioms. But it is not separable.

Example 2. In a Euclidean plane E, let β denote a definite straight line, let A and B denote two definite points of β and let N denote a "half-plane" which is the sum of β and a definite one of the two components of $E - \beta$. If P is a point of β let A_P and B_P denote points of β such that the straight line rays PA_P and PB_P have only P in common and the common part of the straight line rays PB_P and AB is a ray. Let C_P denote a point of N such that the straight line ray PC_P is perpendicular to β. Let W_P denote the set of all straight line rays which start from P and lie, except for P, in the interior of the right angle C_PPB_P. For each ray a of W_P, let $Z(a)$ denote a straight line ray lying, except for P, in the interior of the right angle C_PPA_P and such that the acute angle whose sides are $Z(a)$ and PC_P is congruent to the one whose sides are a and PC_P.

If P is a point of β, a and b are rays of W_P and ϵ is a positive number, let $R_{Pab\epsilon}$ denote a set such that x is an element of it only if either (1) x is the open curve $y + Z(y)$ for some ray y, of the set W_P, such that $y - P$ lies in the interior of the acute angle whose sides are a and b or (2) x is a point which is at a distance less than ϵ from P and which lies either in the interior of the acute angle whose sides are a and b or in the interior of the one whose sides are $Z(a)$ and $Z(b)$.

If P is a point of β, a is a ray of the set W_P and ϵ is a positive number, let $R_{Pa\epsilon}$ denote a set such that x is an element of it only if either (1) x is the ray PC_P or (2) x is the open curve $y + Z(y)$ for some ray y of the set W_P such that $y - P$ lies in the interior of the acute angle whose sides are a and PC_P or (3) x is a point which is at a distance less than ϵ from P and which, in the half-plane N, is separated from $\beta - P$ by the open curve $a + Z(a)$.

Let Σ denote a space such that (1) X is a point of Σ if and only if either X is a point of $E - \beta$ or, for some point P of β, X is PC_P or the open curve $a + Z(a)$ for some ray a of W_P, (2) R is a region of Σ if and only if either, in the half-plane N, R is the interior of some circle containing no point of β or R is $R_{Pab\epsilon}$ for some P, a, b and ϵ or R is $R_{Pa\epsilon}$ for some P, a and ϵ. The space Σ satisfies Axioms 0–4, 5_1, 5_2 and 6. Furthermore it is separable. But it is not completely separable.

[1] *Am. Math. Soc. Colloquium Pub.*, Vol. XIII, New York (1932). The letter S denotes the set of all points.

[2] The symbol H^* denotes the sum of all the point sets of the collection H.

[3] Roberts, J. H., *Bull. Am. Math. Soc.*, **38**, 835–838 (1932).

THE COEFFICIENTS OF STIRLING'S SERIES FOR LOG $\Gamma(x)$

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The asymptotic series

$$\log \Gamma(x) = (\log 2\pi)/2 + (x - 1/2) \log x - x + \sum_{m=1} (c_m/x^{2m-1}) + R,$$

where $c_m \equiv (-1)^{m-1} B_m/[(2m-1)(2m)]$, obviously requires for its evaluation adequate approximations to the numerical values of $\log 2\pi$, $\log x$ and c_m. The desire to apply this series to the extension of my table[1] of $1/n!$ ($\Gamma(n+1) = n!$, n integral), for higher values of n led to the original calculation[2] of $\log \pi$ to 214 significant figures, to the computation of two 137-place tables of natural logarithms for factors of the form $1 \pm a \cdot 10^{-b}$, and finally to the calculation of the table of coefficients (c_m) presented below. Incidentally the table given by Duarte[3] is insufficient for my purposes because it was only designed to furnish about 42 significant figures. This table also has the disadvantage of greatly increasing the number of figures to be written in solving many problems because it is founded upon the base 10 instead of e.

TABLE 1

$c_1 = +0.08\dot{3}$ $\quad c_2 = -0.00\dot{2}7\dot{7}$

$c_3 = +0.000\dot{7}9\ 365\dot{0}$ $\quad c_4 = -0.0005\dot{9}\ 5238\dot{0}$

$c_5 = +0.000\dot{8}4\ 175\dot{0}$ $\quad c_6 = -0.001\dot{9}1\ 752\dot{6}$

$c_7 = +0.00\dot{6}41\ 02\dot{5}$ $\quad c_8 = -0.02955\ 0\dot{6}535\ 94771\ 24183\ 0\dot{0}$

$c_9 = +0.17964\ 43723\ 68830\ 57316\ 49384\ 90015\ 88939\ 66943\ 50254\ 72177$
$17496\ 35526\ 72531\ 00070\ 43753\ 17378\ 41335\ 36455\ 51787\ 96664$
$86477\ 63198\ 84679\ 01780\ 6n$

$c_{10} = -1.392\dot{4}3\ 22169\ 05901\ 11642\ \dot{7}$

$c_{11} = +\ 13.40\dot{2}86\ 40441\ 68391\ 99447\ 89510\ 00690\ 13112\ 49137\ 33609$
$38578\ 32988\ 26777\ 08764\ 66\dot{5}$

$c_{12} = -\ 156.8482\dot{8}\ 46260\ 02017\ 30636\ 51324\ 52088\ 97382\ 81042\ 62886$
$87158\ 25237\ 56436\ 79991\ 5060\dot{7}$

$c_{13} = +\ 2193.10\dot{3}$

$c_{14} = -\ 36108.77125\ 37249\ 89357\ 17326\ 52192\ 42230\ 73648\ 36100\ 46828$
$43763\ 30353\ 34184\ 75947\ 21157\ 93954\ 87441\ 46445\ 29587\ 05832$
$26905\ 1N$

$c_{15} = +\ 6\ 91472.26885\ 13130\ 67108\ 39525\ 07756\ 73467\ 55333\ 40716$
$87798\ 05042\ 31894\ 66571\ 00160\ 99337\ 56763\ 56766\ 45687\ 76915$
$82919\ 61P$

$c_{16} = -\ 152\ 38221.53940\ 74161\ 92283\ 36495\ 88867\ 80518\ 65907\ 65338$
$39342\ 18848\ 82985\ 45224\ 54142\ 94750\ 15812\ 77672\ 35926\ 62871$
$600P$

(*Continued on page 60*)

TABLE 1 (*Continued*)

$c_{17} = +$ 3829 00751.39$\dot{1}\dot{4}$

$c_{18} = -$ 1 08822 66035.78439 10890 15149 16552 51053 74729 43487 98108 19660 44372 05940 96533 94615 80063 08382 24823 18723*n*

$c_{19} = +$ 34 73202 83765.00$\dot{2}\dot{2}\dot{5}$

$c_{20} = -$ 1236 96021 42269.2744$\dot{5}$ 42517 10349 27132 48810 80978 6419$\dot{}$

$c_{21} = +$ 48878 80647 93079.33507 58151 62518 02290 21084 70538 90567 38218 07036 29532 73576 39974 12162 06656 609*N*

$c_{22} = -$ 21 32033 39609 19373.89697 50589 82136 83855 74654 53319 85170 20559 48769 80114 59386 58577 68790 0236*n*

$c_{23} = +$ 1021 77529 65257 00077.56528 76280 53585 50039 40110 32308 90464 93301 81245 07486 20961 38691 88337*P*

$c_{24} = -$ 53575 47217 33002 03610.82770 91919 69204 48484 90405 43658 81649 98678 14010 49235 84272 77075 6*n*

$c_{25} = +$ 30 61578 26370 48834 15043.15$\dot{1}$05 13296 22758 19418 67656 15337 04390 84724 799$\dot{0}$

$c_{26} = -$ 1899 99174 26399 20405 02937.14293 06942 90294 73424 58996 17708 71870 76088 29695 40017 265*n*

$c_{27} = +$ 1 27633 74033 82883 41492 34951.37769 78259 76541 63360 88299 01448 23974 68163 77071 2596*N*

$c_{28} = -$ 92 52847 17612 04163 07230 24234.8347$\dot{6}$ 22779 51933 12434 69174 50365 7$\dot{2}$

$c_{29} = +$ 7218 82259 51856 10297 83605 01873.01637 92248 98404 20259 68876 99474 67538 90375 7*N*

$c_{30} = -$ 6 04518 34059 95856 96774 31482 38754.54728 60661 44395 96719 62074 06301 60809 60*p*

$c_{31} = +$ 542 06704 71570 09454 51934 77814 82610.00136 61202 18579 23497 26775 95628 415*P*

$c_{32} = -$ 51929 57815 31408 19467 00194 76439 18576.84699 70627 13974 47868 03610 3330*p*

$c_{33} = +$ 53 03658 85511 97005 96654 83924 30697 58643.69929 26354 05549 09795 66255*P*

$c_{34} = -$ 5763 32534 81649 64013 89443 58507 80992 55519.07375 62189 05472 63681 6*n*

$c_{35} = +$ 6 65115 57148 48453 93751 65201 45810 55595 10397.39359 45492 89589 09*P*

$c_{36} = -$ 813 73783 58136 68053 87161 72632 09357 56918 40689.16497 38792 624*N*

$c_{37} = +$ 1 05369 66953 35714 18037 54804 92764 18101 89648 37337.50$\dot{1}$14 1552$\dot{5}$

$c_{38} = -$ 144 18180 59996 22062 61805 37780 15118 12809 57033 20636.642$\dot{1}$

$c_{39} = +$ 20817 35652 20895 65462 42480 82412 63562 31131 73432 64150.0*n*

$c_{40} = -$ 31670 22663 48866 61827 41349 55677 42561 34291 80698 3042*p* (3)

$c_{41} = +$ 50700 06461 21113 73431 79264 81531 74876 56762 96280 45*N* (7)

$c_{42} = -$ 85299 72820 30055 18816 20840 05221 62278 88780 70447 (11)

$c_{43} = +$ 15064 17280 93405 98576 69511 73603 79879 07610 1931*n* (15)

$c_{44} = -$ 27893 49470 38316 36871 28838 16863 12781 71234 76*N* (19)

$c_{45} = +$ 54093 50435 28604 15005 76356 18718 84152 58234*N* (23)

$c_{46} = -$ 10975 33782 15085 19855 01678 87261 70795 1671 (27)

$c_{47} = +$ 23274 87620 26184 79173 47864 10320 52184 93 (31)

$c_{48} = -$ 51539 29162 06532 13901 94655 21217 17172*n* (35)

TABLE 1 (*Continued*)

$c_{49} = +$ 11906 21023 08902 26457 68481 61768 7138*p* (39)
$c_{50} = -$ 28668 93896 02966 73696 22642 05419 01*n* (43)
$c_{51} = +$ 71893 07802 33729. 86439 28443 71393*p* (47)
$c_{52} = -$ 18760 69343 05046 71847 89546 2727*N* (51)
$c_{53} = +$ 50904 91469 07510 70481 32915 19*N* (55)
$c_{54} = -$ 14351 42882 84321 71093 65153 5*N* (59)
$c_{55} = +$ 42009 05750 66658 69407 2472*p* (63)
$c_{56} = -$ 12758 58127 22475 75908 433*N* (67)
$c_{57} = +$ 40177 56840 36218 18804 6*n* (71)
$c_{58} = -$ 13110 13631 20068 34587*P* (75)
$c_{59} = +$ 44299 95653 69782 596*P* (79)
$c_{60} = -$ 15492 14069 51735 54*n* (83)
$c_{61} = +$ 56037 64855 62735*p* (87)
$c_{62} = -$ 20953 92414 8581 (91)
$c_{63} = +$ 80952 90300 56*P* (95)
$c_{64} = -$ 32296 33556 0*P* (99) $c_{65} = +$13298 63917*P* (103)
$c_{66} = -$ 56491 165*N* (107) $c_{67} = +$24743 78*n* (111)
$c_{68} = -$ 11170 2*P* (115) $c_{69} = +$5195*n* (119)
$c_{70} = -$ 249*n* (123) $c_{71} = +$12*P* (127)

$\log_e (100!) =$
363.73937 55555 63490 14407 99933 69655 63802 78239 21062
88727 47276 79448 87677 59444 47979 01991 41010 00241 97254
93196 15773 55972 29305 31198 01503 48915 04259 44052 15183
63651 214*n*

$100! =$
$2^{97} \cdot 3^{48} \cdot 5^{24} \cdot 7^{16} \cdot 11^{9} \cdot 13^{7} \cdot 17^{5} \cdot 19^{5} \cdot 23^{4} \cdot 29^{3} \cdot 31^{3} \cdot 37^{2} \cdot 41^{2} \cdot 43^{2} \cdot 47^{2} \cdot 53 \cdot 59 \cdot 61 \cdot 67 \cdot 71 \cdot 73 \cdot 79 \cdot 83 \cdot 89 \cdot 97 =$
933 26215 44394 41526 81699 23885 62667 00490 71596 82643
81621 46859 29638 95217 59999 32299 15608 94146 39761 56518
28625 36979 20827 22375 82511 85210 91686 4×10^{24}

All of the values of c_m here tabulated were worked out very carefully and independently by an assistant and by me. We used two different machines located in widely separated buildings. As far as $m = 62$ the assistant transcribed the values of the Bernoulli numbers (B_m) as calculated and expressed as repeating decimals[4] by Adams while I used the improper fractions[5] having the same author. For values of m greater than 62 the numerators and denominators in Serebrennikoff's earlier table[6] were employed by both of us. The reliability of the borrowed numbers as printed is validated by the following quotation from D. H. Lehmer:[7] "This check assures the correctness not only of the present table but also of the tables of Adams and Serebrennikoff inasmuch as their values were used in computing the table of G_n." The table of c_m as a whole was checked by substituting $x = n = 100$ and finding $\pm \log (100!)$. The antilogarithms were evaluated by means of my tables of $\log (1 \pm a \cdot 10^{-b})$, and they agreed to 141 figures with the previously established values of 100! and 1/100!. These constants

may be found, respectively, at the end of the present new table and under the entry $n = 100$ in the table of reciprocals of factorials.[1]

With one minor exception all of the values of c_m whose recurring periods do not end within the range of the table contain the right number of figures to cause the corresponding terms in Stirling's series to end at the 155th decimal place when $n = 100$. c_{87} has been extended by one digit in order to exhibit both ends of the first period of its repeating decimal. Beginning with c_{40} the number of omitted figures between the last recorded digit and the decimal point is indicated in each case by the number which is enclosed between parentheses.

Estimates of the errors incurred by rounding off the terminal digits may be formed from the somewhat refined convention here introduced. Let c'_m represent the unlimited positive or negative number which, when added to the finitely terminated tabular value of $|c_m|$, will give the true arithmetical value of $B_m/[(2m - 1)(2m)]$, that is, the complete value of infinite extent. c'_m is to be expressed as a decimal such that unit's place coincides with the final digit $f_m(= 0, 1, 2, \ldots, 9)$ of c_m as recorded. When c'_m falls within the narrow range from -0.02 to $+0.02$ no letter follows f_m in the table. If c'_m lies between -0.50 and -0.25 the symbol N succeeds the digit f_m. If c'_m is greater than -0.25 and less than -0.02 the letter n is appended. According to the same scheme the indices p and P correspond, respectively, to the ranges from $+0.02$ to $+0.25$ and from $+0.25$ to $+0.50$. It should now be clear that the symbols are intended to suggest negative and positive corrections, that the capital letters indicate the quarter intervals which are most remote from the center of reference f_m, and that f_m is an enhanced digit whenever it is followed by N or n.

[1] Uhler, H. S., *Trans. Conn. Acad. Arts. Sci.*, **32**, 381–434 (1937).
[2] Uhler, H. S., *Proc. Nat. Acad. Sci.*, **24**, 23–30 (1938).
[3] Duarte, F.-J., *Nouvelles Tables de Log n!*, Geneva, XIII (1927).
[4] *Scientific Papers of John Couch Adams*, **1**, 455–458 (1896).
[5] *Ibid.*, 453.
[6] Serebrennikoff, S. Z., *Mém. Acad. Imp. Sci. St.-Pétersbourg*, **16**, No. 10 (1905).
[7] Lehmer, D. H., *Duke Math. Jour.*, **2**, 460–464 (1936).

OSCILLATIONS OF THE DERIVATIVES OF A FUNCTION

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It is known that if a function is infinitely often differentiable in an open interval and all the derivatives are positive then the function is analytic in

the interval.[1] As a possible generalization of this result Pólya raised the following question:[2] If in an open interval a function is infinitely often differentiable and no derivative changes sign more than a fixed bounded number of times, is the function analytic in the interval? The present paper contains an answer to this question and to several related questions. These results are consequences of a fundamental inequality which relates the magnitude of the first derivative of a function to the number of times some higher derivative changes sign.

THEOREM I. *In an interval* $a - L < x < a + L$ *let*[3] $f(x) \in C^n$, $n \geqq 2$, *and let* $|f(x)| \leqq M$. *If*

$$|f'(a)| \geqq (20n)^{2n} M/L \tag{1}$$

then $f^{(n)}(x)$ *changes sign at least* $n - 1$ *times in the interval.*

The idea in the proof of this theorem is that if the first derivative of a function is "large" at some point then there will be two near-by points where the second derivative is "large" and with different signs. There will then be three near-by points where the third derivative is "large" and with alternating sign, and so on.

THEOREM II. *In the interval* $a < x < b$ *let* $f(x) \in C^\infty$ *and let no derivative change sign more than a fixed bounded number of times. Then* $f(x)$ *is analytic in the interval.*

Consider the case in which the interval is $-1 < x < 1$ and $|f(x)| \leqq 1$. Let no derivative change sign more than $k - 2$ times in the interval. It is shown by induction that for $n = 0, 1, 2, \ldots$ and for $-1 < x < 1$,

$$|f^{(n)}(x)| \leqslant \alpha^n n!(1 - |x|)^{-n} \tag{2}$$

where

$$\alpha = 3(20k)^{2k}.$$

If (2) is true for some n, and x_0 is some point in $(-1, 1)$, then in the subinterval $|x - x_0| \leqslant (1 - |x_0|)(n + 1)^{-1}$ (2) implies that

$$|f^{(n)}(x)| \leqslant 3\alpha^n n!(1 - |x_0|)^{-n};$$

and $f^{(n+k)}(x)$ does not change sign more than $k-2$ times in this subinterval. The induction is then easily completed by use of Theorem I. It follows from (2) that the Taylor's expansion of $f(x)$ about any point in the interval $-1 < x < 1$ converges to $f(x)$ in a complete neighborhood of the point.

A question which naturally arises is whether it is possible to let the number of sign changes of $f^{(n)}(x)$ tend to infinity with n, but sufficiently slowly, and still conclude that the function is analytic. While Theorem I leaves the question open for a finite interval it does say something in this direction for an infinite interval.

THEOREM III. *Let* $f(x) \in C^\infty$ *in* $-\infty < x < \infty$. *Suppose there are finite*

constants $\gamma > 1$ and $L > 0$ such that in every interval of length L the number of sign changes of $f^{(n)}(x)$ is less than $(\log n)(\log \log n)^{-\gamma}$ for $n > n_0$. If

$$\overline{\lim_{x \to \pm \infty}} \frac{1}{|x|} \log |f(x)| < \infty$$

then $f(x)$ is an entire function of order at most one.

In the case in which the number of sign changes of $f^{(n)}(x)$ is uniformly bounded in every interval of length, say, L, it is possible to obtain more precise information concerning the function.

THEOREM IV. *Let $f(x) \in C^\infty$ in $-\infty < x < \infty$. Suppose there are constants $a = [a] > 0$ and $L > 0$ such that $f^{(n)}(x)$ does not change sign more than a times in any interval of length L, $n = 1, 2, 3, \ldots$. If*

$$\overline{\lim_{x \to \pm \infty}} \frac{1}{|x|} \log |f(x)| < \infty$$

then $f(x)$ is an entire function of exponential type.

An entire function is said to be of exponential type if for some constant ρ it satisfies

$$f(z) = O(e^{\rho|z|})$$

uniformly in every direction as $|z| \to \infty$. In Theorem IV, if the function is bounded on the real axis, the proper bound for the constant ρ can be determined in terms of a and L.

Pólya and Wiener have shown[4] that if a function belongs to C^∞ over $-\infty < x < \infty$, is periodic with period p, and no derivative changes sign more than $q = [q]$ times in any interval of length p, then the function is a trigonometric polynomial. It is clear that this result is a consequence of Theorem IV. In a yet unpublished paper Tamarkin has obtained closely related results for functions which are not periodic, but are of integrable square on the real axis.

[1] Bernstein, S., *Leçons sur les propriétés extrémales . . .*, Paris, 1926, p. 190.

[2] At the Stanford University Symposium, August 12, 1941.

[3] The functions considered are real for real values of the variable.

[4] Pólya, G., and Wiener, N., in a paper to appear in the *Trans. Amer. Math. Soc.*